## REMARKS

Claims 31, 34-44, 47-58, 60-61, 65-73, 86-88, and 90-95 are pending in the present application. Claims 1, 4-14, 17-28, and 30 have been cancelled. Claims 31, 40, 44, 56-58, 61 and 91 have been amended and new claims 92-95 have been added. Support for the amendments and new claims can be found in the original claims and in the specification on page 1, lines 17-20, page 4, lines 7-9, page 10, lines 5-8, and page 18, lines 2-7. No new matter has been added.

**35 U.S.C. § 112, second ¶**

Claims 1, 4-14, 17-28, 30-31, 34-44, 47-58, 60-61, 65-73, 86-88, and 90-91 are rejected under 35 U.S.C. § 112, second paragraph, as "being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention."

In particular, the Examiner rejected claims 1 and 31 as being "unclear in the recitation of 'the cell comprises a transgene [integrated] into the genome of the somatic cell' because antecedent basis for 'the cell' is not clearly defined." The Examiner further states "It is not clear if 'the cell' containing the transgene is the germ cell or the purified somatic cell."

Applicants have cancelled claim 1 and amended claim 31 to clarify that the cell is the somatic cell. The cancellation and amendments to these claims obviate this rejection.

The Examiner rejected claims 14, 44, and 61 as being "unclear in the recitation of 'the cell comprises a heterologous nucleic acid sequence which is integrated into the genome of the somatic cell' because antecedent basis for 'the cell' is not clearly defined." The Examiner further stated that "It is not clear if 'the cell' containing the transgene is the germ cell or the purified somatic cell."

Applicants have cancelled claim 14 and amended claims 44 and 61 to clarify that the cell is the somatic cell, thereby obviating this rejection.

**35 U.S.C. § 102**

Claims 1, 4, 5, 7, 12-14, 17, 19, 24-28, 31, 34, 35, 37, 42-44, 47, 49, 54-58, 61, 65, 67, 72, 73, and 86-88 are rejected under 35 U.S.C. § 102(b) as "being anticipated by Archer et al." The Examiner states at pages 5 and 6 of the outstanding office action:

> With respect to the integration of the polynucleotide into the genome of the cell, it should be noted that Archer *et al.* use a retroviral vector system to introduce the transgene into the cells. It is well known in the art that retroviral vectors must integrate into the genome of an infected cell as part of their replication cycle, and as specifically taught on page 6843, top of second column, Archer *et al.* teach that '[I]ntegration of the provirus is dependent on the M phase of the cell cycle' indicating that the retroviral vector used integrates into the genome. Examiners agrees that the reference does not demonstrate that the vector or the transgene is integrated, however inherent to the retroviral vectors used in Archer *et al.* is that the vectors must integrate into the genome.
>
> With respect to the source of the cell, the cell represents a product by process because of the manner it is obtained. Patentability of a product-by-process claim is determined by the novelty and nonobviousness of the claimed product itself without consideration of the process for making it which is recited in the claims.

Claims 1, 4, 5, 7, 12-14, 17, 19, and 24-28 have been cancelled. Applicants respectfully traverse this rejection with regard to the remaining claims. The claims, as amended, are directed to a preparation of embryonic or fetal somatic cells having a trangene (or heterologous sequence) integrated into their genome, and methods of making such cells. As recited in the claims, the transgene (or heterologous sequence) was present and known to be expressed in the transgenic goat from which the embryo or fetus is derived. By virtue of the fact that the transgene or heterologous nucleic acid sequence was present and known to be expressed in the transgenic goat, Applicants claimed preparations have particularly desirable properties. Specifically, the cells of the preparation contain at least one transgene (or heterologous nucleic acid sequence) that is known to be integrated into their genome and expressed within the context of a transgenic goat. Furthermore, the preparations are homogeneous both with respect to the number of transgenes (or heterologous nucleic acid sequences) present within each cell of the preparation and the insertion sites of the transgenes (or heterologous nucleic acid sequences) within each of the cells.

Applicants contend that the presently claimed preparations are clearly distinguishable from the cells of Archer et al. First, the section relied upon by the Examiner to assert that the transgene of Archer et al. is integrated into the genome of the cells refers to *in vivo* methods of infecting cells within the mammary gland – not to *in vitro* cell culture. Second, assuming that the transgene is even integrated into any of the *in vitro* cells, by using a retroviral vector to introduce a transgene into the cells Archer et al. produce a heterogeneous collection of cells in which the number of transgenes present within each cell is ambiguous. Any given cell could have zero, one, two, or more transgenes. In addition, again assuming that the transgene is even integrated into any of the *in vitro* cells, the cells of Archer et al. containing transgenes are likely to have the transgenes integrated in different locations within their genomes, adding to the heterogeneity of the cells. The position at which a transgene is integrated into a cell's genome affects the expression of the gene(s) encoded by the transgene, and thus is relevant to the utility of the cell. Applicants are interested in *in vitro* cells that are useful for the production of transgenic goats using cloning technology. The desirable properties of the presently claimed preparations make these cells highly suitable for the production of transgenic goats using cloning technology, whereas the cells of Archer et al. are much less suitable for such purposes. For example, using the cells of Archer et al. to clone goats, one would inevitably produce large numbers of non-transgenic goats and transgenic goats that do not express the transgene, thereby greatly reducing efficiency. Archer et al. do not recognize these deficiencies of their *in vitro* cell preparations because they are not interested in cloning transgenic goats.

Given the clear differences between the cells of Archer et al. and the presently claimed preparations, Archer et al. do not anticipate the composition claims. With regards to the method claims, Archer et al. do not teach any of the recited steps and, therefore, clearly do not anticipate these claims. For the reasons discussed above, Applicants request that the Examiner withdraw this rejection.

Claims 61, 65-73, 86-88, 90 and 91 are rejected under 35 U.S.C. 102(e) as "being anticipated by Strelchenko et al." The Examiner states at pages 7 and 8 of the outstanding office action:

> Applicant is correct in differentiating totipotent and pluripotent cells, however it is the totipotent cell which gives rise to the pluripotent cell, and thus, the totipotent cell is capable of generating any somatic cell in the entire animal as demonstrated b[y] the teaching of Strelchenko *et al.* Strelchenko *et al.* specifically teach multiple embodiments to their invention as summarized in figures 3 and 4. Specifically, in figure 4, the flow chart clearly indicates the isolation of immortalized cells and screening for transgene expression. Further, Strelchenko *et al.* teach the various stages of the embryo and fetus development, as well as developed cells and indicate that cells can be obtained from any of these sources and put into cell culture. Strelchenko *et al.* teach a method of establishing a cultured cell (column 44; Example 2). Examples [of] specific promoters, in particular milk protein promoters (column 12; lines 30-37), specific trangenes encoding specific polypeptides such as hormones, enzymes, plasma proteins and immunoglobulins are recited throughout the specification (for example column 36; lines 7-63). Finally, transgenic cells can be prepared from transgenic animals (columns 50-52; Example 8). Thus, the teachings of Strelchenko *et al.* anticipate the claims...

Applicants respectfully traverse this rejection. The claims are directed to methods of preparing an embryonic or fetal caprine somatic cell line. The methods include obtaining a somatic cell from an embryonic or fetal goat wherein the somatic cell has a heterologous nucleic acid sequence integrated into its genome. The embryonic or fetal goat is derived from a germ cell of a transgenic goat known to have and express the heterologous nucleic acid sequence. The somatic cell is then cultured in a suitable medium such that a somatic cell line is obtained. As pointed out previously, the claimed methods result in a homogeneous cell line with regard to the number of sequences integrated and the location of integration, and hence the expression, of the heterologous nucleic acid sequence. Strelchenko et al. clearly do not teach or suggest such methods.

The Examiner argues that "the totipotent cell gives rise to the pluripotent cell and, thus, the totipotent cell is capable of generating any somatic cell in the entire animal." Nevertheless, Applicants point out that, although totipotent cells may be capable of generating any somatic cell in an entire animal, they do so within the context of an entire animal. Techniques for differentiating totipotent cells *in vitro* such that they form specific cell types are limited in the art, and Strelchenko et al. fail to teach any method of differentiating their totipotent cells outside the context of a developing embryo. Thus, Strelchenko et al. provide no reason to believe that their totipotent cells could be used to produce the claimed preparations.

Applicants agree that Strelchenko et al. generally disclose obtaining cells from any number of sources and at a variety of different developmental stages. However, Strelchenko et al. fail to provide any connection between cells obtained from a fetus or embryo, cells obtained from a goat, and cells into which a heterologous nucleic acid sequence has been introduced. Instead, Strelchenko et al. provide a laundry list of eighteen different animals to obtain a cell. In an unrelated section of the reference, Strelchenko et al. provided embryonic and fetal cells in a list of thirty-three different cell types. In yet another section, Strelchenko et al. note that cells can be unmodified or modified. An example of a modified cell is one that includes a transgene. How the transgene is introduced into the cell leads to another list of techniques. Nowhere in any of these disparate sections are the claimed methods disclosed. There is no disclosure in Strelchenko et al. of obtaining a purified preparation of embryonic or fetal caprine somatic cells that comprise a heterologous nucleic acid sequence integrated into their genome disclosed. There is also no disclosure in Strelchenko et al. of obtaining these specific cells from an embryo or fetus derived from a germ cell of a transgenic goat known to have and express the transgene. Strelchenko et al. provide absolutely no indication that cells from these different and specific sources have any particular value in producing totipotent cells, let alone in producing a preparation of somatic cells. In fact, it is quite apparent from the specification that Strelchenko et al. are really concerned with bovine cells, specifically adult bovine cells (see, for example, column 2, third paragraph). Throughout the specification of Strelchenko et al., there are numerous references to using bovine cells as the source of the totipotent cells, while there is not a single specific reference to using embryonic goat cells or fetal goat cells as the source.

Since Strelchenko et al. fail to disclose methods of producing the preparations of the present invention, and also fail to specifically disclose the tissue source used to produce the cells of the present invention, it is impossible to conclude that Strelchenko et al. anticipate the present invention. Accordingly, Applicants request that the Examiner withdraw this rejection.

**35 U.S.C. § 103**

Claims 1, 4, 5, 7-14, 17, 19-28, 30, 31, 34, 35, 37-44, 47, 49-58, and 60 are rejected under 35 U.S.C. § 103(a) as "being unpatentable over Archer et al. and Amoah et al." The Examiner states at pages 9 and 10 of the outstanding office action:

As noted above in the 35 USC 102 rejection above, Archer et al. anticipate the claimed invention encompassed by claims 1, 4, 5, 7, 12-14, 17, 19, 24-28, 31, 34, 35, 37, 42-44, 47, 49, 54-58, 61, 65, 67, 72, 73, 86-88. The basis of the present rejection is to teach other promoters and transgenes which were known in the art and/or already used to target transgene expression in transgenic goats as taught in Amoah et al. In light of the level of skill and knowledge in the art of transgenic animals, evaluating either of the two references as a whole, it would have been obvious to combine the teachings of the two references to obtain a purified embryonic or fetal caprine somatic cell wherein the cell contains a transgene with the embodiments recited in claims 1, 4, 5, 7-14, 17, 19-28, 30, 31, 34, 35, 37-44, 47, 49-58, 60.

Claims 1, 4, 5, 7, 12-14, 17, 19, and 24-28 have been cancelled. Applicants respectfully traverse this rejection with regard to the remaining claims. As discussed above, even if it is assumed that the transgene of Archer et al. integrates into the genome of some of the *in vitro* cultured cells, the resulting cells will be heterogeneous with respect to the number of transgenes integrated into the genome and the position (and hence expression) of the integrated transgenes. In contrast, Applicants cell preparations are homogeneous in that each cell contains a transgene (or heterologous nucleic acid molecule) that was present and known to be expressed in the transgenic goat used to produce the embryo or fetus from which the cells were obtained. Thus, Archer et al. disclose cells that are clearly distinct from, and lack the desirable characteristics of, Applicants' cell preparations.

Amoah et al. discuss various advances in goat reproduction including in vitro fertilization of caprine oocytes, culturing embryos to the morulae through blastocyst stage in vitro and transfer of such embryos into a recipient. Nowhere in Amoah et al. is purification of an embryonic or fetal somatic cell even taught or suggested. Moreover, Amoah et al. do not disclose anything about homogeneous preparations of goat cells or the desirability of such preparations. Consequently, there is nothing in Amoah et al. that compensates for the deficiencies of Archer et al. Accordingly, Applicants request that the Examiner withdraw this rejection.

Claims 1, 4-14, 17-28, 30, 31, 34-44, 47-58, 60, 61, 65-73, 86-88, 90 and 91 are rejected under 35 U.S.C. § 103(a) as "being unpatentable over Archer et al. and Amoah et al. as applied

to claims 1, 4, 5, 7-14, 17, 19-28, 30, 31, 34, 35, 37-44, 47, 49-58, 60 above, and further in view of Strelchenko et al." The Examiner states at page 11 of the outstanding office action:

> Clearly from the overlapping claims included in the 35 USC 102 rejections the references teach overlapping subject matter which anticipates specific embodiments of the claimed invention. Presently, Strelchenko et al. was used to make obvious the deficiencies of specific embodiments not specifically taught in Archer et al. nor Amoah et al. As noted above, Strelchenko et al. teach the creation of transgenic animals and the methods to isolate and culture cells from animals for use in the methodology. Further, it was noted that Strelchenko et al. teach multiple embodiments of their invention as summarized in Figures 3 and 4 and detailed throughout the entire specification.

Claims 1, 4, 5, 7, 12-14, 17, 19, and 24-28 have been cancelled. Applicants respectfully traverse this rejection with regard to the remaining claims. As discussed above, the amended claims are directed to preparations of embryonic or fetal caprine somatic cells and methods of producing such preparations. The methods include obtaining a somatic cell from an embryonic or fetal goat wherein the somatic cell has a heterologous nucleic acid sequence integrated into its genome. The embryonic or fetal goat is derived from a germ cell of a transgenic goat known to have and express the heterologous nucleic acid sequence. The somatic cell is then cultured in a suitable medium such that a somatic cell line is obtained. The claimed methods result in a preparation of cells that is homogeneous with regard to the number of sequences integrated and the location of integration (and hence the expression) of the heterologous nucleic acid sequence.

As discussed above, even if it is assumed that the transgene of Archer et al. is integrated into some of the cultured cells, the cells disclosed by Archer et al. are at best a heterogeneous mixture. Furthermore, Archer et al. are interested in using retroviral vectors to infect goat mammary cells *in vivo* by introducing the viral vector into mammary ducts. Archer et al. use cultured goat cells simply for the purpose of determining whether their retroviral transgene construct is likely to be expressed in goat mammary cells *in vivo*. Archer et al. do not suggest any further uses for cultured goat cells. Moreover, Archer et al. report *in vivo* integration of their viral vectors in the mammary gland. Thus, there is nothing in Archer et al. which would motivate a skilled artisan to change to disclosed methods or to consider any methods of

enhancing the properties of the cultured cells, especially since these cells were just intermediaries for optimizing the *in vivo* procedure of Archer et al.

Strelchenko et al. disclose methods of producing totipotent cells for the production of cloned animals. However, the totipotent cells of Strelchenko et al. are clearly distinct from the somatic cells of Applicants' cell preparations. Furthermore, there is nothing in Strelchenko et al. that discloses the production of embryonic or fetal caprine somatic cell preparations, nor is there an indication that such preparations might be desirable. As discussed above, Strelchenko et al. merely provide long lists of various cell types in disparate sections of that reference. The Examiner has randomly chosen specific elements from these lists in an attempt to recreate the claimed invention. There is nothing in Strelchenko et al. which would motivate a skilled artisan to combine specific elements of these various lists to arrive at the claimed invention.

As discussed above, Amoah et al. generally discusses advances in goat reproduction. This references provides absolutely no teaching or suggestion of purifying embryonic or fetal caprine somatic cells. In fact, Amoah et al. do not discuss cultured goat cells at all. Therefore, the teaching of Amoah et al. add nothing which would make up for the deficiencies of Archer et al. or Strelchenko et al.

Since there is nothing in the combination of Archer et al. and Amoah et al. that suggest that embryonic or fetal caprine somatic cell preparations are desirable, there is no way to combine the three references such that it would be obvious and desirable to try to adapt the methods of Strelchenko et al. so as to produce the presently claimed embryonic or fetal caprine somatic cell preparations.

Consequently, none of the presently pending claims are obvious in view of the teachings of Archer et al., Amoah et al. or Strelchenko et al., either alone or in combination. Applicants, therefore, request that the Examiner withdraw this rejection.

Attached is a marked-up version of the changes being made by the current amendment.

Applicant asks that all claims be allowed. Enclosed is a check for the Petition for Extension of Time fee. Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date: 12/05/01

Laurie Butler Lawrence
Reg. No. 46,593

Fish & Richardson P.C.
225 Franklin Street
Boston, Massachusetts 02110-2804
Telephone: (617) 542-5070
Facsimile: (617) 542-8906

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**Version with markings to show changes made**

In the claims:

Claims 1, 4-14, 17-28, and 30 have been cancelled.

Claims 31, 40, 44, 56-58, 61 and 91 have been amended as follows:

31. A purified preparation of [an] embryonic or fetal caprine somatic [cell] cells obtained from an embryonic or fetal goat derived from a germ cell of a transgenic goat, wherein the somatic [cell comprises] cells comprise a transgene integrated into [the] their genome [of the somatic cell] and wherein the transgene was also present and known to be expressed in the transgenic goat.

40. The preparation of claim 39, wherein the promoter is selected from the group consisting of a β-casein promoter, a β-lactoglobin promoter, whey acid protein promoter and lactalbumin promoter.

44. A purified preparation of [an] embryonic or fetal caprine somatic [cell] cells obtained from an embryonic or fetal goat derived from a germ cell of a transgenic goat, wherein the somatic [cell comprises] cells comprise a heterologous nucleic acid sequence [which is] integrated into [the] their genome[ of the somatic cell] and wherein the heterologous nucleic acid sequence was also present and known to be expressed in the transgenic goat.

56. The preparation of claim 31, wherein the somatic [cell is a fibroblast] cells are fibroblasts.

57. The preparation of claim 56, wherein the [fibroblast is] fibroblasts are [a] primary [fibroblast] fibroblasts.

58. The preparation of claim 56, wherein the [fibroblast is a] fibroblasts are primary derived [fibroblast] fibroblasts.

61. A method of preparing an embryonic or fetal caprine somatic cell line comprising:

(a) obtaining a somatic cell from an embryonic or fetal goat derived from a germ cell of a transgenic goat, wherein the somatic cell comprises a heterologous nucleic acid sequence[ which is ]integrated into [the]its genome [of the somatic cell] and wherein the heterologous nucleic acid sequence was also present and known to be expressed in the transgenic goat; and

(b) culturing the somatic cell in a suitable medium such that a somatic cell line is obtained.

91. A method of preparing a genetically engineered cell line, comprising:

(a) inseminating a female recipient with semen from a transgenic non-human animal known to have a transgene present and expressed;

(b) obtaining a transgenic non-human embryo from the recipient;

(c) obtaining a somatic cell from the embryo; and,

(d) culturing the cell in a suitable medium,

such that a somatic cell line is obtained.

Add claims 92-95.

-- 92. (New) The preparation of claim 31, wherein the cells are obtained from an embryonic goat on or after day 10 of embryogenesis.

93. (New) The preparation of claim 31, wherein the preparation is in an airtight container.

94. (New) The preparation of claim 44, wherein the cells are obtained from an embryonic goat on or after day 10 of embryogenesis.

95. (New) The preparation of claim 44, wherein the preparation is in an airtight container.--

Amended Claims

**Version with markings to show changes made**

In the claims:

Please cancel claims 2, 3, 15, 16, 29, 32, 33, 45, 46, 59, 62-64, 74-85 and 89.

Please amend claims 1, 4, 5-7, 9, 10, 12, 13, 14, 17, 18, 21, 22, 25, 30, 31, 34-44, 47-58, 60-61, 65-67, 69, 70, 72, 73, 90 and 91 as follows:

-- 1. (Amended) A purified embryonic or fetal caprine somatic cell obtained from an embryonic or fetal goat derived from a germ cell obtained from a transgenic goat, wherein the cell comprises a transgene integrated into the genome of the somatic cell.

Archer et al
CHE1 cells

2. (Cancel) The cell of claim 1, wherein the cell comprises a transgene.

3. (Cancel) The cell of claim 2, wherein the transgene is integrated into the genome of the somatic cell.

4. (Amended) The cell of claim [2] 1, wherein the transgene is a heterologous transgene.

5. (Amended) The cell of claim 1, wherein the transgene [includes] comprises a nucleic acid sequence encoding a human [sequence] polypeptide.

6. (Amended) The cell of claim [2] 1, wherein the transgene is a knockout, or a knockin [or other event which disrupts expression of a caprine gene].

7. (Amended) The cell of claim [2] 5, wherein the transgene [is] further comprises a promoter wherein the nucleic acid sequence is under the control of [a] the promoter.

9. (Amended)The cell of claim 8, wherein the tissue-specific promoter is a [milk-specific] promoter preferentially expressed in mammary gland epithelial cells.

10. (Amended) The cell of claim 9, wherein the [milk-specific] promoter is selected from the group consisting of a β-casein promoter, a β-lactoglobin promoter, whey acid protein promoter and lactalbumin promoter.

12. (Amended) The cell of claim [2] 5, wherein the [transgene] nucleic acid sequence encodes a polypeptide selected from the group consisting of a hormone, an immunoglobin, a plasma protein, and an enzyme.

13. (Amended) The cell of claim [2] 5, wherein the [transgene] nucleic acid sequence encodes a polypeptide selected from the group consisting of an α-1 proteinase inhibitor, an alkaline phosphotase, an angiogenin, an extracellular superoxide dismutase, a fibrogen, a glucocerebrosidase, a glutamate decarboxylase, a human serum albumin, a myelin basic protein, a proinsulin, a soluble CD4, a lactoferrin, a lactoglobulin, a lysozyme, a lactoalbumin, an erythropoietin, a tissue plasminogen activator, a human growth factor, an antithrombin III, an insulin, a prolactin, and an α1-antitrypsin.

14. (Amended) [The] A purified embryonic or fetal caprine somatic cell obtained from an embryonic or fetal goat derived from a germ cell obtained from a transgenic goat, [of claim 1,] wherein the cell comprises a heterologous nucleic acid sequence which is integrated into the genome of the somatic cell.

15. (Cancel) The cell of claim 15, wherein the nucleic acid is integrated into the genome of the somatic cell.

16. (Cancel) The cell of claim 14, wherein the nucleic acid is a heterologous nucleic acid.

17. (Amended) The cell of claim [16] 14 wherein the heterologous nucleic acid sequence [includes] encodes a human [sequence] polypeptide.

18. (Amended) The cell of claim 14, wherein the nucleic acid is a knockout, or a knockin [or other event which disrupts the expression of a caprine gene].

21. (Amended) The cell of claim 20, wherein the tissue-specific promoter is a [milk specific] promoter preferentially expressed in mammary gland epithelial cells.

22. (Amended) The cell of claim 21, wherein the [milk-specific] promoter is selected from the group consisting of a β-casein promoter, a β-lactoglobin promoter, whey acid protein promoter and lactalbumin promoter.

25. (Amended) The cell of claim 14, wherein the [transgene] nucleic acid encodes a polypeptide selected from the group consisting of an α-1 proteinase inhibitor, an alkaline phosphotase, an angiogenin, an extracellular superoxide dismutase, a fibrogen, a glucocerebrosidase, a glutamate decarboxylase, a human serum albumin, a myelin basic protein, a proinsulin, a soluble CD4, a lactoferrin, a lactoglobulin, a lysozyme, a lactoalbumin, an erythropoietin, a tissue plasminogen activator, a human growth factor, an antithrombin III, an insulin, a prolactin, and an α1-antitrypsin.

29. (Cancel) The cell of claim 1, wherein the cell is obtained from an embryonic or fetal goat derived from a germ cell obtained from a transgenic goat.

30. (Amended) The cell of claim [29] 1, wherein the germ cell is sperm from a transgenic goat.

31. (Amended) A purified preparation of an embryonic or fetal caprine somatic cell obtained from an embryonic or fetal goat derived from a germ cell obtained from a transgenic goat, wherein the cell comprises a transgene which is integrated into the genome of the somatic cell.

32. (Cancel) The cell of claim 31, wherein the cell comprises a transgene.

33. (Cancel) The cell of claims 32, wherein the transgene is integrated into the genome of the somatic cell.

34. (Amended) The [cell] preparation of claim [32] 31, wherein the transgene is a heterologous transgene.

35. (Amended) The [cell] preparation of claim 34, wherein the heterologous transgene [includes] comprises a nucleic acid sequence encoding a human [sequence] polypeptide.

36. (Amended) The [cell] preparation of claim [32] 31, wherein the transgene is a knockout, or a knockin [or other event which disrupts the expression of a caprine gene].

37. (Amended) The [cell] preparation of claim [32] 35, wherein the transgene further comprises a promoter wherein the nucleic acid is under the control of [a] the promoter.

38. (Amended) The [cell] preparation of claim 37, wherein the promoter is a tissue specific promoter.

39. (Amended) The [cell] preparation of claim 38, wherein the tissue-specific promoter is a [milk-specific] promoter preferentially expressed in mammary gland epithelial cells.

40. (Amended) The [cell] preparation of claim 39, wherein the [milk-specific] promoter is selected from the group consisting of a β-casein promoter, a β-lactoglobin promoter, whey acid protein promoter and lactalbumin promoter.

41. (Amended) The [cell] preparation of claim 37, wherein the promoter is a caprine promoter.

42. (Amended) The [cell] preparation of claim [32] 35, wherein the [transgene] nucleic acid encodes a polypeptide selected from the group consisting of a hormone, an immunoglobin, a plasma protein, and an enzyme.

43. (Amended) The [cell] preparation of claim [32] 35, wherein the [transgene] nucleic acid encodes a polypeptide selected from the group consisting of an α-1 proteinase inhibitor, an alkaline phosphotase, an angiogenin, an extracellular superoxide dismutase, a fibrogen, a glucocerebrosidase, a glutamate decarboxylase, a human serum albumin, a myelin basic protein, a proinsulin, a soluble CD4, a lactoferrin, a lactoglobulin, a lysozyme, a lactoalbumin, an erythropoietin, a tissue plasminogen activator, a human growth factor, an antithrombin III, an insulin, a prolactin, and an α1-antitrypsin.

44. (Amended) [The cell of claim 31] A purified preparation of an embryonic or fetal caprine somatic cell obtained from an embryonic or fetal goat derived from a germ cell of a transgenic goat, wherein the cell comprises a heterologous nucleic acid integrated into the genome of the somatic cell.

45. (Cancel) The cell of claim 44, wherein the nucleic acid is integrated into the genome of the somatic cell.

46. (Cancel) The cell of claim 44, wherein the nucleic acid is a heterologous nucleic acid.

47. (Amended) The [cell] preparation of claim [46] 44, wherein the heterologous nucleic acid [includes] encodes a human [sequence] polypeptide.

48. (Amended) The [cell] preparation of claim 44, wherein the nucleic acid is a knockout, or a knockin [or other event which disrupts the expression of a caprine gene].

49. (Amended) The [cell] preparation of claim 44, wherein the nucleic acid is under the control of a promoter.

50. (Amended) The [cell] preparation of claim 49, wherein the promoter is a tissue-specific promoter.

51. (Amended) The [cell] preparation of claim 50, wherein the tissue-specific promoter is a [milk-specific] promoter preferentially expressed in mammary gland epithelial cells.

52. (Amended) The [cell] preparation of claim 51, wherein the [milk-specific] promoter is selected from the group consisting of a β-casein promoter, a β-lactoglobin promoter, whey acid protein promoter and lactalbumin promoter.

53. (Amended) The [cell] preparation of claim 49, wherein the promoter is a caprine promoter.

54. (Amended) The [cell] preparation of claim 44, wherein the [transgene] nucleic acid sequence encodes a polypeptide selected from the group consisting of a hormone, an immunoglobin, a plasma protein, and an enzyme.

55. (Amended) The [cell] preparation of claim 44, wherein the [transgene] nucleic acid sequence encodes a polypeptide selected from the group consisting of an α-1 proteinase inhibitor, an alkaline phosphotase, an angiogenin, an extracellular superoxide dismutase, a fibrogen, a glucocerebrosidase, a glutamate decarboxylase, a human serum albumin, a myelin basic protein, a proinsulin, a soluble CD4, a lactoferrin, a lactoglobulin, a lysozyme, a lactoalbumin, an erythropoietin, a tissue plasminogen activator, a human growth factor, an antithrombin III, an insulin, a prolactin, and an α1-antitrypsin..

56. (Amended) The [cell] preparation of claim 31, wherein the somatic cell is a fibroblast.

57. (Amended) The [cell] preparation of claim 56, wherein the fibroblast is a primary fibroblast.

58. (Amended) The [cell] preparation of claim 56, wherein the fibroblast is a primary derived fibroblast.

59. (Cancel) The cell of claim 31, wherein the cell is obtained from an embryonic goat derived from a germ cell obtained from a transgenic goat.

60. (Amended) The [cell] preparation of claim [59] 31, wherein the germ cell is sperm from a transgenic goat.

61. (Amended) A method of preparing an embryonic or fetal caprine somatic cell line comprising:

(c) obtaining a somatic cell from an embryonic or fetal goat derived from a germ cell of a transgenic goat, wherein the cell comprises a heterologous nucleic acid sequence which is integrated into the genome of the somatic cell; and

(d) culturing the cell in a suitable medium

such that a somatic cell line is obtained.

62. (Cancel) The method of claim 61, wherein the cell line is a genetically engineered cell line.

63. (Cancel) The method of claim 62, wherein the cell comprises a transgene integrated into its genome.

64. (Cancel) The method of claim 63, wherein the transgene is a heterologous transgene.

65. (Amended) The method of claim [64] 61, wherein the heterologous [transgene] nucleic acid sequence encodes [includes] a human [sequence] polypeptide.

66. (Amended) The method of claim [63] 61, wherein the [transgene] sequence is a knockout, or a knockin [or other event which disrupts expression of a caprine gene].

67. (Amended) The method of claim [63] 61, wherein the [transgene] nucleic acid sequence is under the control of a promoter.

69. (Amended) The method of claim 88, wherein the tissue-specific promoter is a [milk-specific] promoter preferentially expressed in mammary gland epithelial cells.

70. (Amended) The method of claim 69, wherein the [milk-specific] promoter is selected from the group consisting of a β-casein promoter, a β-lactoglobin promoter, whey acid protein promoter and lactalbumin promoter.

72. (Amended) The method of claim [63] 61, wherein the [transgene] nucleic acid sequence encodes a polypeptide selected from the group consisting of a hormone, an immunoglobulin, a plasma protein, and an enzyme.

73. (Amended) The method of claim [63] 61, wherein the [transgene] nucleic acid sequence encodes a polypeptide selected from the group consisting of an α-1 proteinase inhibitor, an alkaline phosphotase, an angiogenin, an extracellular superoxide dismutase, a fibrogen, a glucocerebrosidase, a glutamate decarboxylase, a human serum albumin, a myelin basic protein, a proinsulin, a soluble CD4, a lactoferrin, a lactoglobulin, a lysozyme, a lactoalbumin, an erythropoietin, a tissue plasminogen activator, a human growth factor, an antithrombin III, an insulin, a prolactin, and an α1-antitrypsin.

74. (Cancel) The method of claim 62, wherein the cell comprises a heterologous nucleic acid.

75. (Cancel) The method of claim 74, wherein the nucleic acid is integrated into the genome of the somatic cell.

77. (Cancel) The method of claim 74, wherein the nucleic acid is a heterologous nucleic acid.

78. (Cancel) The method of claim 76, wherein the heterologous nucleic acid includes a human sequence.

79. (Cancel) The method of claim 74, wherein the nucleic acid is a knockout, knockin or other event which disrupts expression of a caprine gene.

80. (Cancel) The method of claim 74, wherein the nucleic acid is under the control of a promoter.

81. (Cancel) The method of claim 79, wherein the promoter is a tissue-specific promoter.

82. (Cancel) The method of claim 80, wherein the tissue-specific promoter is a milk-specific promoter.

83. (Cancel) The method of claim 81, wherein the milk-specific promoter is selected from the group consisting of a β-casein promoter, a β-lactoglobin promoter, whey acid protein promoter and lactalbumin promoter.

84. (Cancel) The method of claim 79, wherein the promoter is a caprine promoter.

85. (Cancel) The method of claim 74, wherein the nucleic acid encodes a polypeptide selected from the group consisting of a hormone, an immunoglobulin, a plasma protein, and an enzyme.

86. (Cancel) The method of claim 74, wherein the nucleic acid encodes a polypeptide selected from the group consisting of an α-1 proteinase inhibitor, an alkaline phosphotase, an angiogenin, an extracellular superoxide dismutase, a fibrogen, a glucocerebrosidase, a glutamate

decarboxylase, a human serum albumin, a myelin basic protein, a proinsulin, a soluble CD4, a lactoferrin, a lactoglobulin, a lysozyme, a lactoalbumin, an erythropoietin, a tissue plasminogen activator, a human growth factor, an antithrombin III, an insulin, a prolactin, and an α1-antitrypsin.

89. (Cancel) The method of claim 61, wherein the cell is obtained from an embryonic or fetal goat derived from a germ cell obtained from a transgenic goat.

90. (Amended) The method of claim [89] 61, wherein the germ cell is sperm from a transgenic goat.

91. (Amended) A method of preparing a genetically engineered cell line, comprising:

(e) inseminating a female recipient with semen from a transgenic non-human animal;

(f) obtaining a transgenic non-human embryo from the recipient;

(g) obtaining a somatic cell from [a] the embryo; and,

(h) culturing the cell in a suitable medium,

such that a somatic cell line is obtained.